REMARKS

Withdrawn Rejections

Applicants thank the Examiner for carefully considering Applicants' claim amendments and arguments submitted March 23, 2005, and for withdrawing rejections made in the previous Office Action.

Claim Rejections under 35 U.S.C. § 102

Claims 1 and 25 are rejected under 35 U.S.C. 102(a) as being anticipated by Bittner *et al.* (Nature, Vol. 406, 3 August 2000, pages 536-560). Applicants note that *Bittner* possesses a priority date of August 3, 2000. All of the inventors of the present application are listed as authors on *Bittner*. Because manuscripts are typically submitted to scientific journals well in advance of the publication date, it is intuitive that the subject matter of the claims, to the extent that it might be read on by *Bittner*, was invented prior to the publication date of *Bittner*.

In addition, Applicants have included declarations pursuant to 37 CFR 1.131 from each of the inventors that provides evidence of prior invention, including reduction to practice. In particular, the declarations include Exhibit "A" is a copy of an email sent from inventor Michael Bittner to co-inventors of the present application that has attached thereto a draft manuscript of the *Bittner* reference. The manuscript attached to the email of Exhibit A is in substantially the same form as the published manuscript. The email of Exhibit A predates the *Bittner* reference, and includes details of the methods described in part or in whole at least in independent claims 1, 4, 26, and 28 (with like features contained in respective dependent claims as well). Dates and sensitive information (*e.g.*, email addresses) have been redacted in the document in accordance with applicable USPTO rules.

The actual manuscript attached to the email of the Exhibit A is not included in Exhibit A because it is not in an electronic form that can be accessed by the Applicants at this time. The co-inventor Michael Bittner is no longer employed by the National Institutes of Health, and therefore is not able to access the electronic records that contain the manuscript.

As further evidence that the present invention was reduced to practice prior to publication of the *Bittner* reference, Exhibit "B" is attached to the Declarations. Exhibit "B" is a copy of the PowerPoint® presentation that was developed by at least one of the

co-inventors. The PowerPoint® presentation predates the *Bittner* reference, and includes details of the methods described in part or in whole at least in independent claims 1, 4, 26, and 28 (with like features contained in respective dependent claims as well). In particular, the graph of the gene expression patterns on Slide 5 of the document is identical or substantially similar to FIG. 2B of the instant patent application that identifies genes that discriminate melanoma clusters, including the top 22 genes obtained by multi-dimensional scaling (MDS) analysis ranking genes according to their impact on minimizing cluster volume and maximizing center-to-center inter-cluster distance.

In addition, the MDS graph depicted on slide 4 of the document of Exhibit B is identical or substantially similar to FIG. 1B of the instant patent application, that shows the clustering of gene expression data, and indicates in particular a MDS three-dimensional plot of all 31 cutaneous melanoma samples showing major clustering of 19 samples, and the remaining 12 outlying samples. One skilled in the art would be able to arrive at the method of claim 1 by reviewing the data and suggestions of the PowerPoint® presentation of Exhibit B.

The Examiner is relying on similar data from the *Bittner* reference as that shown in the document of Exhibit B to reject the instant claims. The inventors of the present application developed the subject matter of the *Bittner* reference prior to the publication date of the *Bittner* reference.

As additional evidence that the present invention was reduced to practice prior to publication of the *Bittner* reference, Exhibit "C" is attached hereto. Exhibit "C" is a copy of the invention disclosure submitted to the legal department of Agilent Technologies, the Assignee of record. The invention disclosure includes details of the methods described in part or in whole at least in independent claims 1, 4, 26, and 28 (with like features contained in respective dependent claims as well). In particular, the invention disclosure discusses on page 1 a method of diagnosing an aggressive form of cancer, based on evaluating expression of WNT5A gene. On page 2 of the invention disclosure, the inventors indicate that the WNT5A's role in melanoma metastasis was suggested in the conclusions of the *Bittner* reference. Therefore, because the inventors are all listed as authors on the *Bittner* reference, the inventors reduced the invention to practice prior to the publication date of the *Bittner* reference. Dates have been redacted in the document in accordance with applicable USPTO rules.

Thus, because *Bittner* possesses a priority date that is unsatisfactory as anticipatory art, Applicants respectfully request that the rejection of independent

claims 1 and 25 be withdrawn. For at least these reasons the other pending claims are also allowable over *Bittner*.

Claim Rejections under 35 U.S.C. §112, First Paragraph

Claims 1, 4, and 25 are rejected under 35. U.S.C. §112, first paragraph, as based on a disclosure which is allegedly not enabling. Specifically, the Office Action alleges the following:

> Comparing increased expression of Wnt5a in a test sample of a tumor compared to the gene expression profile of Wnt5a from a cluster of pair-matched tumor samples appears critical or essential to the practice of the invention but is not included in the claims. Hence, the currently claimed method is not enabled by the disclosure. [cite]. Currently, the claimed method only compares the increased expression of Wnt5a in the test sample compared to its expression in a tumor. The teachings of the specification suggest that the latter is an oversimplification. For example, the specification teaches (page 12, line 18) that the expression data from a particular marker gene is analyzed using statistical methods in order to determine the phenotype or characteristic of a particular tumor or cancer. As such, the inventors did not merely compare the increased expression of Wnt5a to its expression in a tumor, but rather appeared to employ complex quantitative and comparative measurements via gene expression profiling that employed both hierarchical and non-hierarchical clustering algorithms (see page 22-24). The specification further teaches that on the basis of the linear correlation of global gene expression in Fig. 1, Figs. 2 and 3 illustrate the approach used to guide 'gene cluster' interpretation empirically. Nowhere is it taught or suggested that the overexpression of Wnt5a can be merely compared to its expression in "a tumor". Thus, it would appear that the claimed method is not enabling because a feature which is taught as critical in the specification and is not recited in the claims should result in a rejection of such claim....

Office Action at 3-4. Applicants respectfully traverse. In particular, Applicants have not cited anywhere in the specification that comparing increased expression of Wnt5a in a test sample of a tumor compared to the gene expression profile of Wnt5a from a cluster of pair-matched tumor samples is critical or essential to the practice of the claimed methods.

As a general rule, "[t]he enablement requirement of 35 U.S.C. §112, ¶1 requires that the specification adequately discloses to one skilled in the relevant art how to make, or in the case of a process, how to carry out, the claimed invention without undue experimentation." *Process Control Corp. v. Hydreclaim Corp.*, 190

F.3d 1350, 52 USPQ2d 1029 (Fed. Cir. 1999). As discussed below, Applicants have provided a plethora of support in the specification as to how to carry out the methods of claims 1 and 4. Indeed, the statistical methods used and described in the specification are not necessary to understand the methods claimed in independent claims 1 and 4. The statistical analyses performed merely confirm that the result of the methods of claims 1 and 4 are valid; they are not necessary in order to perform the methods of claims 1 and 4.

The present case is analogous to that set forth in *Mycogen Plant Sci., Inc. v. Monsanto Co.*, 252 F.3d 1306, 58 USPQ2d 1891 (Fed. Cir.), *reh'g den.*, 59 USPQ2d 1852 (Fed. Cir. 2001). In *Mycogen*, the accused infringer asserted that the claims were too broad to be enabled by the specification, which provides only one example of an embodiment of the invention. The court in that case rejected the argument stated that "The specification of the... patent, however, includes more than just a single example: it contains codon usage ***tables, recommendations on the preferred level*** of homology, ***and means for calculating deviation*** of the frequency of preferred codon usage." *Id.* (emphasis added). Although the present technology is are different areas of the biotechnology art, Applicants in the instant specification have similarly provided a table with its measurements, indications of the levels of invasive ability, cell motility, and vasculogenic mimicry that indicate whether a cancer is aggressive, as well as their statistical means for calculating the significance of the results. Thus, Applicants have enabled one of ordinary skill in the art to practice the method of the claims without undue experimentation.

Nevertheless, to advance prosecution and to facilitate allowance of the claims, Applicants have amended claims 1 and 4 to recite other steps that can be performed in practicing the claimed invention. The specification enables one skilled in the art to practice the methods of the claims. Support and enablement for the claims can be found at least at Table 1. Table 1 includes data from various melanoma cell lines and compares various characteristics of these cell lines. For example, data comparing invasive ability, vasculogenic mimicry, gel contractions, cell motility, and the ability to close an *in vitro* scratch wound are provided. The legend to Table 1 provides information on how the data for each characteristic was obtained.

As described in the specification, expression patterns from 31 melanomas were used to group cells according to similar expression patterns of certain genes (paragraph 54). The cells in the melanoma primary cluster group (Group A) showed

reduced invasive ability compared to the non-clustered melanoma cells (Group B)(see Table 1). Specifically, *Wnt5a* is expressed at high levels in Group B cells.

UACC-903 cells in Group B or the non-cluster melanoma cells show a range from 3.8 ± 0.3% to 10.7 ± 0.03% invasive ability. This range is higher than about 3.5% invasive ability, as recited in claim 1. Group A melanoma cells show invasive ability from 2.1 ± 0.2% to 3.2 ± 0.2%, a range with is lower than about 3.5% invasive ability.

Moreover, Group B melanoma cells are distinguishable from Group A melanoma cells in part because Group B melanoma cells show a greater invasive ability, and are therefore more aggressive. Figure 2B shows that Group B cells strongly express *Wnt5a*, whereas Group A cells weakly express *Wnt5a*. Thus, the specification provides both enablement and written description for a method of diagnosing an aggressive form of cancer comprising providing a genetic sample from a first tumor having less than about 3.5% invasive ability, measuring *Wnt5a* expression in the first genetic sample, providing a genetic sample from a test sample of a second tumor, measuring *Wnt5a* expression in the second genetic sample, and analyzing expression of *Wnt5a* wherein increased expression of *Wnt5a* in the test sample of the second tumor, compared to *Wnt5a* expression in a tumor having less than about 3.5% invasive ability, indicates the second tumor is aggressive and has the potential to metastasize. Accordingly, Applicants respectfully request that the rejection of claim 1 be withdrawn.

With respect to claim 4, the specification provides both enablement and a written description, in at least the passages referred to above, for a method of diagnosing an aggressive form of cancer comprising measuring *Wnt5a* expression in a first tumor having non-detectable or no vasculogenic mimicry, providing a genetic sample from a test sample of a second tumor, determining expression of *Wnt5a* in the second tumor wherein increased expression of *Wnt5a* in the test sample of the second tumor compared to *Wnt5a* expression in the first tumor having non-detectable or no vasculogenic mimicry indicates the second tumor is aggressive, *etc.* Accordingly, Applicants respectfully request that the rejection of claim 4 also be withdrawn.

Newly Added Claims

Claims 26-33 have been newly added to further define and/or clarify the scope of the claims.

Support for new claim 26 can be found at least in Table 1. Specifically, the cell motility for case no. UACC-1012 of Group B (the non-clustered group) is 122 ± 11.30 (the lowest value of which is 110.7). As noted above, it has been determined that the cancers of Group B are aggressive. The features recited in claim 26 have clear written support in, and are clearly enabled by, the specification. Claim 27 is allowable for at least the reason that it depends from independent claim 26.

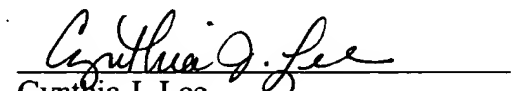
Support for new claim 28 can be found at least in FIGs. 1-3, Table 1, and description related thereto. The features recited in claim 28 have clear written support in, and are clearly enabled by, the specification. Specifically, the Examiner seemed to propose a portion of the language of claim 28 in the Office Action on page 3. Claims 29-33 are allowable for at least the reason that they depend upon independent claim 28.

No new matter has been added by the additional claims, and therefore a new search is not required to examine the newly added claims. For at least this and other reasons, Applicants respectfully request that newly added claims 26-33 be allowed.

CONCLUSION

In light of the foregoing amendments and for at least the reasons set forth above, Applicants respectfully submit that all rejections have been traversed, rendered moot, and/or accommodated, and that the now pending claims 1, 4, and 25-33 are in condition for allowance. Favorable reconsideration and allowance of the present application and all pending claims are hereby courteously requested. If, in the opinion of the Examiner, a telephone conference would expedite the examination of this matter, the Examiner is invited to call the undersigned agent at (770) 933-9500.

Respectfully submitted,



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